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09/684,794	10/10/2000	Rong Jian Yang		1968
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Raymond Yat Chin Chao			EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

	Application N .	Applicant(s)				
	09/684,794	YANG ET AL.				
Office Action Summary	Examiner	Art Unit				
	" Neon" Phuong Huynh	1644				
The MAILING DATE of this communication appears on the cover sheet with the correspondence address Period for Reply						
A SHORTENED STATUTORY PERIOD FOR REPLY THE MAILING DATE OF THIS COMMUNICATION. - Extensions of time may be available under the provisions of 37 CFR 1.13 after SIX (6) MONTHS from the mailing date of this communication. - If the period for reply specified above is less than thirty (30) days, a reply If NO period for reply is specified above, the maximum statutory period w - Failure to reply within the set or extended period for reply will, by statute, - Any reply received by the Office later than three months after the mailing earned patent term adjustment. See 37 CFR 1.704(b).	6(a). In no event, however, may a reply be tin within the statutory minimum of thirty (30) day ill apply and will expire SIX (6) MONTHS from cause the application to become ABANDONE	nely filed rs will be considered timely. the mailing date of this communication. D (35 U.S.C. § 133).				
Status						
1) Responsive to communication(s) filed on <u>10 December 2001</u> .						
 2a) ☐ This action is FINAL. 2b) ☐ This action is non-final. 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11, 453 O.G. 213. 						
Disposition of Claims						
4) Claim(s) 13-27 is/are pending in the application.						
4a) Of the above claim(s) is/are withdrawn from consideration.						
5) Claim(s) is/are allowed.						
6)⊠ Claim(s) <u>13-27</u> is/are rejected.						
7) Claim(s) is/are objected to.						
8) Claim(s) are subject to restriction and/or election requirement.						
Application Papers						
9) The specification is objected to by the Examiner.						
10)☐ The drawing(s) filed on is/are: a)☐ accepted or b)☐ objected to by the Examiner.						
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).						
11)☐ The proposed drawing correction filed on is: a)☐ approved b)☐ disapproved by the Examiner.						
If approved, corrected drawings are required in reply to this Office action.						
12) The oath or declaration is objected to by the Examiner.						
Priority under 35 U.S.C. §§ 119 and 120						
13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).						
a) ☐ All b) ☐ Some * c) ☐ None of:						
1. Certified copies of the priority documents						
2. Certified copies of the priority documents have been received in Application No						
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)). * See the attached detailed Office action for a list of the certified copies not received.						
14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).						
a) The translation of the foreign language provisional application has been received. 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.						
Attachment(s)						
1) Notice of References Cited (PTO-892) 2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s)	5) Notice of Informal P	(PTO-413) Paper No(s) latent Application (PTO-152)				

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DETAILED ACTION

- 1. Claims 13-27 are pending.
- 2. The objection of the specification is hereby withdrawn in view of the supplemental specification filed 12/10/01.
- 3. The objection of Claims 1, 3-5 is hereby withdrawn in view of the amendment filed 12/10/01.
- 4. The rejection of Claims 1-7 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is hereby withdrawn in view of the amendment filed 12/10/01.
- The rejection of Claims 1 and 3-4 under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (US Pat No. 5,367,054, Nov 1994; PTO 892) and or Akita et al (J. of Food Science: 57(3): 629-634; PTO 892) in view of Hatta et al (Caries Res 31(4): 268-74, 1997, PTO 892) or Hamada et al (Microbiol Immunol 22(6): 301-314, 1978; PTO 892) or Natarajan et al (Dev Comp Immunol 8(4): 845-54, 1984; PTO 892) is hereby withdrawn in view of the amendment filed 12/10/01.
- 6. The following new grounds of objections and rejections are necessitated by the amendment filed 12/10/01.
- 7. The disclosure is objected to because of the following informality: The "0.22 μ " on page 5 line 26 is missing the unit. It should have been "0.22 μ m". Appropriate correction is required.
- 8. Claim 17 (c-3) is objected to because of typographical error "fro". Appropriate correction is required.
- Claims 21-25 are objected to because of typographical error "22 μ"; it should have been "22 μm".
 Appropriate correction is required.

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10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 18-26 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 18-26 as written represent a departure from the specification and the claims as originally filed. The specification and the claims as originally filed do not provide a clear support for "eliminating bacteria".

- 12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

 The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.
- 13. Claims 13-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "1-2:1" as recited in claim 13(a) and 14(a-4) is ambiguous. The specification on page 5 line 9 discloses mixing equal volume of type c and d, which is 1:1 ratio.

The recitation of "2:1" in claim 26 is ambiguous and indefinite. The specification on page 5 line 9 discloses mixing equal volume of type c and d, which is 1:1 ratio.

The recitation of "step (b)" in claim 16 has no antecedent base in base claim 14. Base claim 14 recites the step (a) comprises the steps of (a-1) through (a-5).

The recitation of "step (c)" in claim 18 has no antecedent base in base claim 14. Base claim 14 recites the step (a) comprises the steps of (a-1) through (a-5).

The recitation of "step (c)" in claim 19 has no antecedent base in base claim 15. Base claim 15 recites the step (b) comprises the steps of (b-1) through (b-3).

The recitation of "step (c)" in claim 20 has no antecedent base in base claim 16. Base claim 16 recites the step (b) comprises the steps of (b-1) through (b-3).

The recitation of "pouring protein peaks" in claims 21-25 and 27 is ambiguous. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

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The recitation of "step (e)" in claim 22 has no antecedent base in base claim 17. Base claim 17 recites the step (c) comprises the steps of (c-1) through (c-5).

The recitation of "step (e)" in claim 23 has no antecedent base in base claim 18. Base claim 18 recites the step (c) comprises the steps of (c-1) through (c-5).

The recitation of "step (e)" in claim 24 has no antecedent base in base claim 19. Base claim 19 recites the step (c) comprises the steps of (c-1) through (c-5).

The recitation of "step (e)" in claim 25 has no antecedent base in base claim 20. Base claim 20 recites the step (c) comprises the steps of (c-1) through (c-5).

The recitation of "immunizing hens with said streptococcus mutans to get eggs" in claim 13 is indefinite and ambiguous. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
- This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).
- 16. Claims 13- 20 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,367,054 (of record, Nov 1994; PTO 892) or Akita et al (of record, J. of Food Science: 57(3): 629-634; PTO 892) each in view of US Pat No. 4,4324,782 (April 1982, PTO 892), Hatta et al (of record, Caries Res 31(4): 268-74, 1997, PTO 892), Harlow et al (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 96-98),

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Hamada et al (of record, Microbiol Immunol 22(6): 301-314, 1978; PTO 892), Grasssman et al (FASEB J 4(8): 2528-32, May 1990; PTO 892) and US Pat No 4,400,376 (Aug 1983, PTO 892).

The '054 patent teaches a method of preparing egg immunoglobulin Y (IgY) against bacteria Streptococcus mutans (See column 8, line 26, in particular) wherein the method steps comprises immunizing hens with a mixture of bacteria such as Streptococcus mutans by injection each time at two weeks intervals (See column 8, lines 9-66, in particular), collecting the eggs after hyperimmunization, extracting crude IgY by water dilution such as diluting the separated egg yolk with 5-30 times deionized water, preferably with 4-6 fold of distilled water (See column 5, lines 38-40, column 2, line 24, in particular), adjusting the diluted yolk solution to pH about 4-6 (See column 5, lines 48-49, in particular), standing the diluted yolk solution at 3-4 °C for at least 2 hr for phase separation (See column 2, line 24, in particular), centrifuging the diluted yolk solution at high speed at about 2500-30,000 rpm to obtain a supernatant (See column 5, line 44, in particular), concentrating the supernatant which is the crude IgY by ultrafiltration (See column 5 line 65-68 bridging column 6, lines 1-2, Example 5, in particular). Following ultrafiltration, the partially pure IgY retentate can be dried by lyophilization (freeze dry) or spray dry (See column 12, example 12, in particular) and/or further purified by sequential ion exchange chromatography such as DEAE column chromatography (See entire document, column 10 line 69 bridging column 11; column 6, line 15; column 6 line 55, Fig 1, in particular), and cation exchange chromatography such as Sephadex column chromatography using the appropriate buffer for the specific column (See column 11, Example 6, example 8, in particular). For ion exchange chromatography, the column matrix that is suitable for large scale IgY purification includes DEAE (diethylaminoethyl)-Sepharose or DEAE-Sephadex wherein the IgY is eluted with DEAE ion exchange buffer (eluant) which is a sodium phosphate buffer containing about 0.01-0.4M NaCl as the final salt concentration (See entire document, column 5 line 49, in particular). Other suitable anion-exchange chromatography materials as well as the selection of using these materials are known to those ordinary skilled in the art (See column 6, line 55, in particular). The '054 patent further teaches egg yolk is a very good source of specific antibodies, the advantages of IgY antibody production is about 100-150 mg/egg and maintenance of higher levels of specific antibodies is relatively easy (See column 1, lines 34-54, in particular). Claims 17 (c-1), 18 (c-1), 19 (c-1) and 20 (c-1) are included in this rejection because the reference diluting the yolks with 5-31 fold water includes the claimed diluting with 4-6 fold-distilled water. Claims 17 (c-2), 18 (c-2), 19 (c-2) and 20 (c-2) are included in this rejection because the reference pH about 4-6 includes

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the claim pH 4.5-6.5. Claims 17 (c-3), 18 (c-3), 19 (c-3) and 20 (c-3) are included in this rejection because standing yolk solution for 20-30 hours for phase separation is within the purview of one of ordinary skill in the art at the time the invention was made to practice the claimed invention.

Akita *et al* teach a preparation method of extracting egg IgY immunoglobulin by water dilution with six-fold of water, adjusting the pH 5.0 to 5.2, let it stands for at least 2 hr before high speed centrifugation (See entire document, page 629 Materials and Methods) to yield 100mg pure IgY per egg by a combination of ultrafiltration, gel filtration with Sephacryl S-200 using 0.1M phosphate buffer at pH 7.0 and DEAE-Sephacel anion exchange chromatography equilibrate with the appropriate starting buffer (See entire document, Materials and Methods, page 630, in particular) wherein the choice of column depends on the amount of IgY to be purified. Furthermore, Akita *et al* teach that the optimal dilution of egg yolk with six-fold of water at a pH 5.0 and incubation time of 6 hour at 4 °C gave an IgY recovery of 93-96% (See page 632, right column second paragraph). Akita *et al* teach that the use of gel filtration or anion exchange as the final steps should be most efficient. The advantages of this protocol are that the procedure is simple, rapid and produces high yields of active IgY (See page 633, right column last paragraph, in particular).

The claimed invention as recited in claim 13(a) differs from the reference only by the recitation of preparing streptococcus mutans antigens by mixing streptococcus mutans type c and type d in a ratio of 1-2: 1.

The claimed invention as recited in claim 13(e) differs from the reference only by the recitation of applying the active eluates on Sephadex G-200 column and eluting with phosphate buffer containing 0.05-0.2M of NaCl.

The claimed invention as recited in claim 14 differs from the reference only by the recitation of separately cultivating s mutans type c and type d in a culture medium for 2 to 3 days; collecting bacteria by centrifugation, washing said bacteria 4 to 6 times with 0.05-0.2M phosphate buffered saline at pH 6-7 and heating at 50-60 °C for 25 to 35 minutes, mixing said s mutants type c and type d in a ratio of 1:1 or 2:1 and adding Freund's adjuvant equal to total volume of said streptococcus mutans type c and d with high speed homogenized.

The '782 patent teaches antibody against Streptococcus mutans generated from bovine milk can inhibit dental caries (See entire document). The '782 patent teaches cultivating S. mutans such as strains AHT, BHT, 10499 and 6715 separately in culture for 48 hours (2 days) at

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37 °C, collecting the bacteria by centrifugation, wash bacteria 5 times with distilled water, and heat killed bacteria by heating at 56 °C for two hours, mixing the different strains at 1:1 ratio by suspending the heat killed bacteria in physiological saline solution for immunization (See column 3, lines 16-66, in particular).

Hatta et al teach Streptococcus mutants serotype c specific IgY immunoglobulin for against dental carries in humans (See entire document, page 269 Materials and Methods, in particular). The reference method steps comprise culturing S mutans type c (MT8148 c) in culture medium at 37 °C, collecting bacteria by centrifugation, washing the reference bacteria at least 3 times with 0.05M phosphate buffer, immunizing hens, collecting eggs from 4 to 22 weeks after the first immunization, purifying Streptococcus mutants IgY antibodies by anion exchange column chromatography such as DEAE-Sephacel, Gel filtration, Ultrafiltration (See page 158, column 1, in particular). Hatta et al further teach Streptococcus mutants specific IgY inhibits S mutans adherence to saliva-coated hydroxyapatite and is an effective method to control the colonization of mutans streptococci in the oral cavity of humans (See abstract, in particular).

Hamada *et al* teach Streptococcus mutans such as serotype c and d which were isolated from Japanese children with dental caries (See entire document, Table 5 in particular) and serotypes c, d, e, and f develop plaque on the molar teeth and induced dental caries in SD rat (See page 306, in particular) while serotype d strain preferentially developed smooth surface caries as well as caries of fissure origin (See page 312, first paragraph).

Gassmann *et al* teach egg yolk of immunized chicken is a rich and inexpensive source of specific polyclonal antibodies and antigen specific antibodies appears 20 days after immunization, reached a plateau after 30 days and remained high until at least day 81 (See abstract, in particular).

Harlow et al teach Freund's adjuvant is one the best adjuvants for stimulating strong and prolonged responses for antibody production and the most commonly use adjuvant (See page 98, in particular). The method step comprises mixing the antigen with equal volume of the adjuvant oil vigorously until a thick emulsion develops by using a tissue homogenizer for large volumes (See page 98, in particular).

The '376 patent teaches purification of immunoglobulin such as anti-B2M simply by initial immunosorbent purification using gel filtration on material such as Sephadex (dextran based) follows by a gel filtration step using material such as Sephadex G-200 to separate the immunoglobulin and impurity on the basis of molecular weight (See column 5, line 11-32, lines

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61-68, in particular). The '376 patent further teaches the "best results are obtained with material such as those marketed under the trade names Sephadex G-200" using phosphate buffered saline (See column 5, lines 65-68, column 10, line 39-40, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to prepare immunoglobulin IgY against dental caries bacteria such as *Streptococcus mutans* type c as taught by the '054 patent, Hatta *et al* and *Streptococcus mutans* serotype d as taught by Hamada *et al* against dental carries as taught by Hatta *et al*, Hamada *et al* or the '782 patent comprising culturing said bacteria as taught by Hatta *et al*, Hamada *et al* or the '782 patent by immunizing hens as taught by '054 patent, Hatta *et al* or Gassmann *et al* with said bacteria in the presence of Freund's adjuvant as taught by Harlow *et al* and extracting IgY by water dilution and a combination of anion exchange chromatography as taught by the '054 patent, Hatta *et al*, Akita *et al* and Natarjan *et al* and gel filtration using Sephadex G-200 as taught by the '376 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Hatta et al teach Streptococcus mutants specific IgY inhibits S mutans adherence to saliva-coated hydroxyapatite and is effective method to control the colonization of mutans streptococci in the oral cavity of humans (See abstract, in particular). The '782 patent teaches antibody against Streptococcus mutans generated from bovine milk can inhibit dental caries (See entire document). Hamada et al teach serotype d strain of Streptococcus mutants preferentially developed smooth surface caries as well as caries of fissure origin (See page 312, first paragraph). The '054 patent further teaches egg yolk is a very good source of specific antibodies, the advantages of IgY antibody production is about 100-150 mg/egg and maintenance of higher levels of specific antibodies is relatively easy (See column 1, lines 34-54, in particular). Gassmann et al teach egg yolk of immunized chicken is a rich and inexpensive source of specific polyclonal antibodies and antigen specific antibodies appears 20 days after immunization, reached a plateau after 30 days and remained high until at least day 81 (See abstract, in particular). Harlow et al teach Freund's adjuvant is one the best adjuvants for stimulating strong and prolonged responses for antibody production and Freund's adjuvant is the most commonly use adjuvant (See page 98, in particular). Akita et al teach that the use of gel filtration or anion exchange as the final steps should be most efficient and the advantages are that the procedure is simple, rapid and produces high yields of

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active IgY (See page 633, right column last paragraph, in particular). The '376 patent teaches immunoglobulin can be simply purify by initial immunosorbent purification using gel filtration on material such as Sephadex follows by a gel filtration step using material such as Sephadex G-200 to separate on the basis of molecular weight and the best results are obtained with material such as those marketed under the trade names Sephadex G-200 (See column 5, line 11-32, lines 61-68, in particular).

Claims 21-25 and 27 rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,367,054 (of record, Nov 1994; PTO 892) or Akita et al (of record, J. of Food Science: 57(3): 629-634; PTO 892) each in view of US Pat No. 4,4324,782 (April 1982, PTO 892) and Hatta et al (of record, Caries Res 31(4): 268-74, 1997, PTO 892), Harlow et al (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 96-98), Hamada et al (of record, Microbiol Immunol 22(6): 301-314, 1978; PTO 892), Grasssman et al (FASEB J 4(8): 2528-32, May 1990; PTO 892) and US Pat No 4,400,376 (Aug 1983, PTO 892) as applied to claims 13, 17, 18, 19, 20 and 26 above, and further in view of US Pat No. 4,136,094 (Jan 1979, PTO 892).

The teachings of the '054 patent, Akita et al, the '782 patent, Hatta et al, Harlow et al, Hamda et al, Grassman et al, and the '376 patent have been discussed supra.

The claimed invention as recited in claims 21-25 and 27 differs from the references only by the recitation of pouring protein peaks, estimating antibody with ELISA and sterilizing by 0.22 µm membrane filtration.

Hatta *et al* teach analyses of IgY preparations and estimating the activity of S. mutans IgY by ELISA (See page 269, Analyses of IgY Preparation, page 270, Enzyme-Linked Immunosorbent Assay (ELISA), in particular).

The '094 patent teaches sterilizing immunoglobulin by filtration through a 0.22 μ m membrane for intravenous injection (See column 10, lines 60-62, Fig 1, claims of '094, in particular). The '094 patent teaches that the advantages of filtration through a 0.22 μ m membrane are (1) simplicity, (2) speed, (3) the method can be easily scale up and (4) the products are free from virus and can be isolated in higher yields (See column 3, lines 1-14, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to identify the active fraction of the IgY by ELISA as taught by

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Hatta et al and filter sterilizes the isolated immunoglobulin through a 0.22 μ m membrane as taught by the '094 patent.

One having ordinary skill in the art would have been motivated to do this because the '094 patent teaches filtration through a 0.22 µm membrane are (1) simple, (2) speed, (3) the method can be easily scale up and (4) the products are free from virus and can be isolated in higher yields for intravenous injection (See column 3, lines 1-14, in particular).

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

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20. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.

Patent Examiner

Technology Center 1600

February 25, 2002

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER

SUPERVISORY PATENT EXAMINER GROUP-1890 / G & &